CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-286

Medical Review(s)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Clinical Review

NDA: 21-286 (olmesartan)

Sponsor: Sankyo Pharma Inc

Submission: Original NDA; second review of once- vs. one-or-twice-daily dosing.

Review date: April 4, 2002

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

The original secondary review (dated 4 October 2001) recommended once-daily dosing only. This supplementary review re-examines the support for a twice-daily option.

The original recommendation was based on the inability to distinguish once- and twice-daily regimens in ABPM study 204, for which hourly average data are shown in Figure 1.

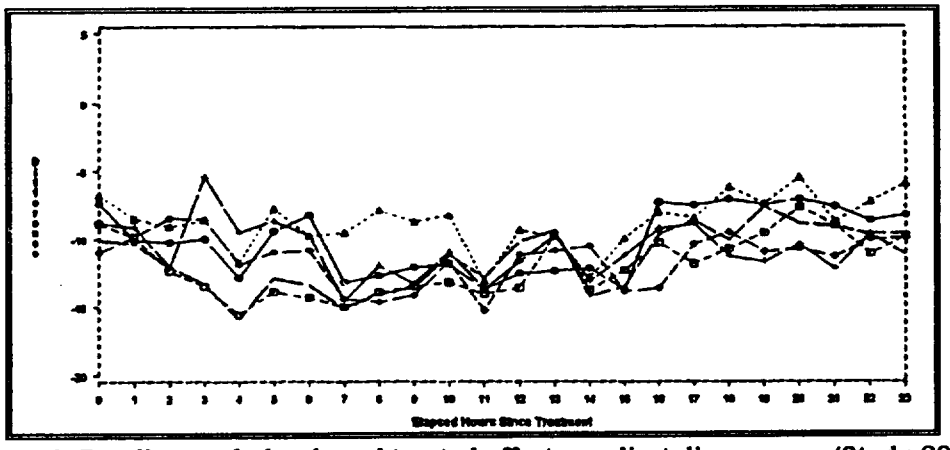

Figure 1. Baseline- and placebo-subtracted effects on diastolic pressure (Study 204).
Curves are hourly average ABPM for doses of 5, 20, and 80 mg qd, and 2.5, 5, and 40 mg bid.

When the 80-mg data are extracted from this figure, and one looks at the hourly average systolic and diastolic pressure differences between once- and twice-daily dosing, the results are as shown in Figure 2.

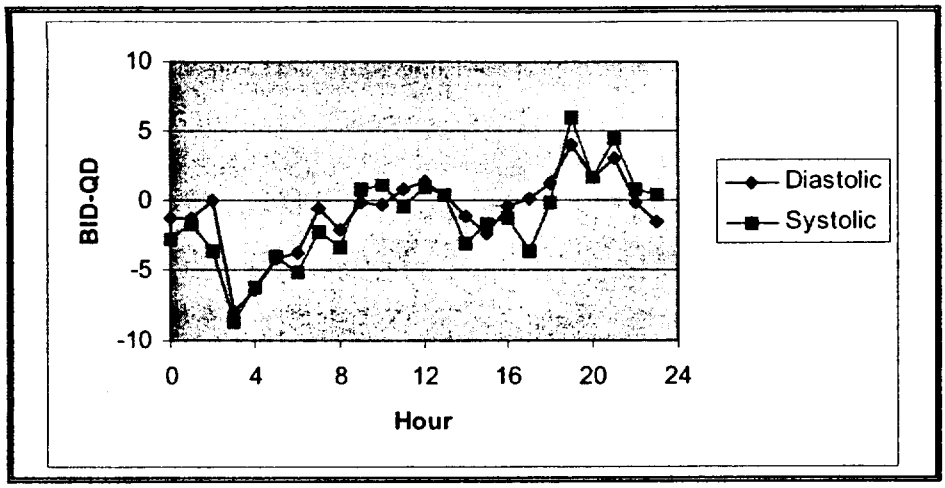

Figure 2. Difference in effects of once- and twice-daily dosing at 80 mg.

The same data as in Figure 1 were used here. The figure shows the effect of twice-daily dosing minus the effect of once daily dosing. Times are from the QD dose.

The dip around hour 3 shows a larger effect of the 40-mg dose compared with the 80-mg dose, and the peak around hour 20 shows a larger effect of the 80-mg dose 20 hours earlier, despite the fact that the second 40-mg dose was given about hour 12. These effects are the opposite of what would be expected, so they are likely not reproducible.

The curves for the 80-mg dose are isolated in Figure 3.

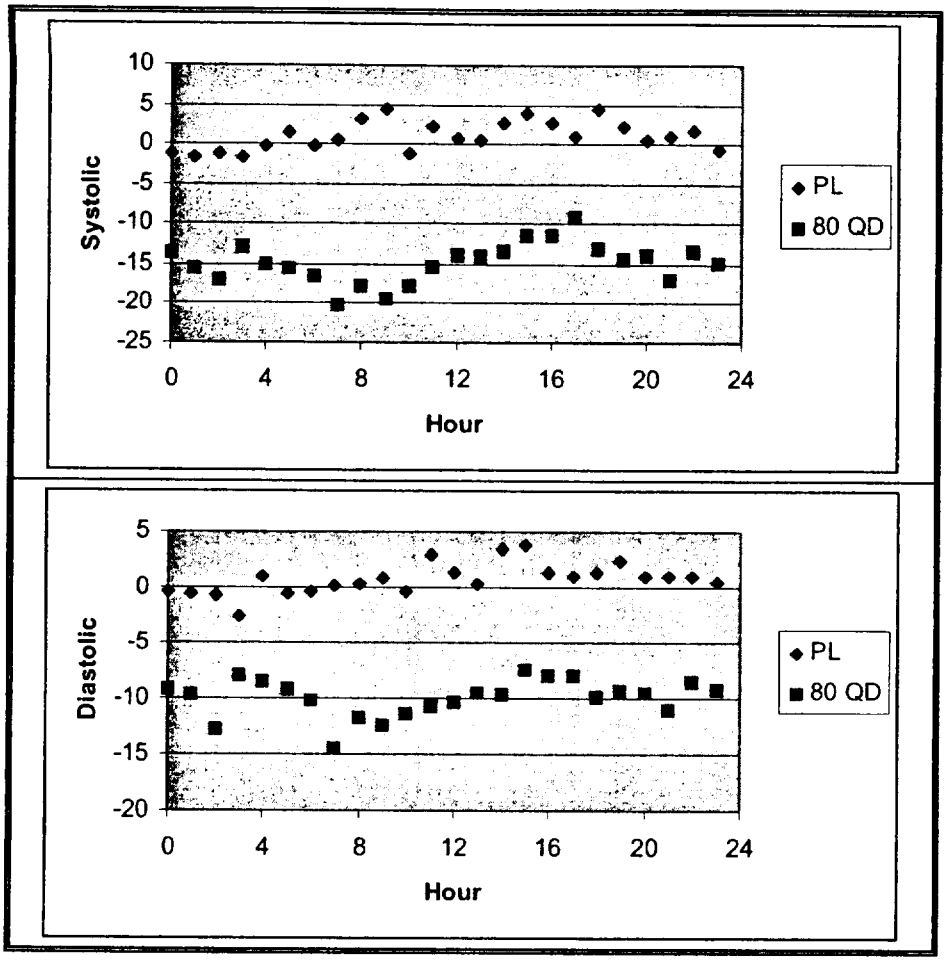

Figure 3. Systolic and diastolic pressure changes from baseline in study 204.

Data are shown for the placebo and once-daily 80-mg doses. The amount of variation in the placebo group is similar to the amount of variation in the 80-mg dose.

No waning of treatment effect is evident in these data.

Although the usual advice is to get to the highest dose once-daily and then consider twice-daily dosing, it is informative to look at the ABPM time course for a lower dose, so Figure 2 and Figure 3 are recapitulated below in Figure 4 and Figure 5, respectively, for the 5-mg dose (also from Study 204).

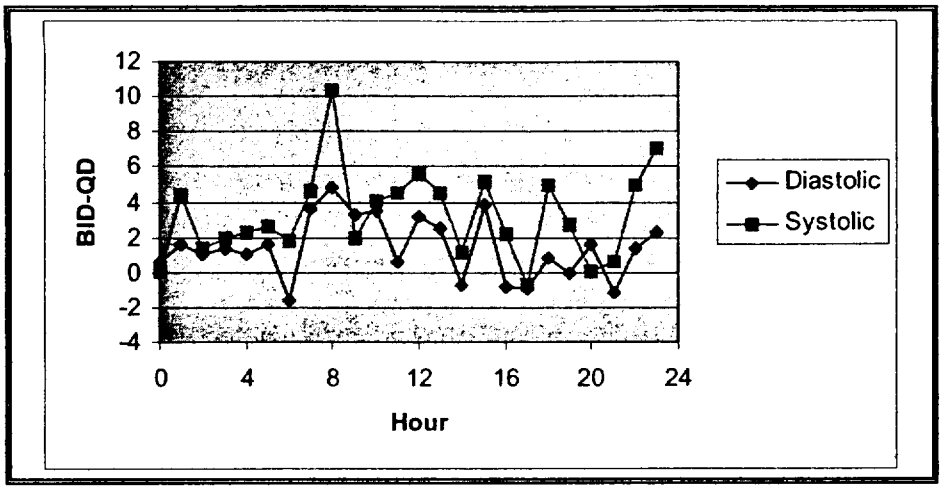

Figure 4. Difference in effects of once- and twice-daily dosing at 5 mg.

The same data as in Figure 1 were used here. The figure shows the effect of twice-daily dosing minus the effect of once-daily dosing. Times are from the QD dose.

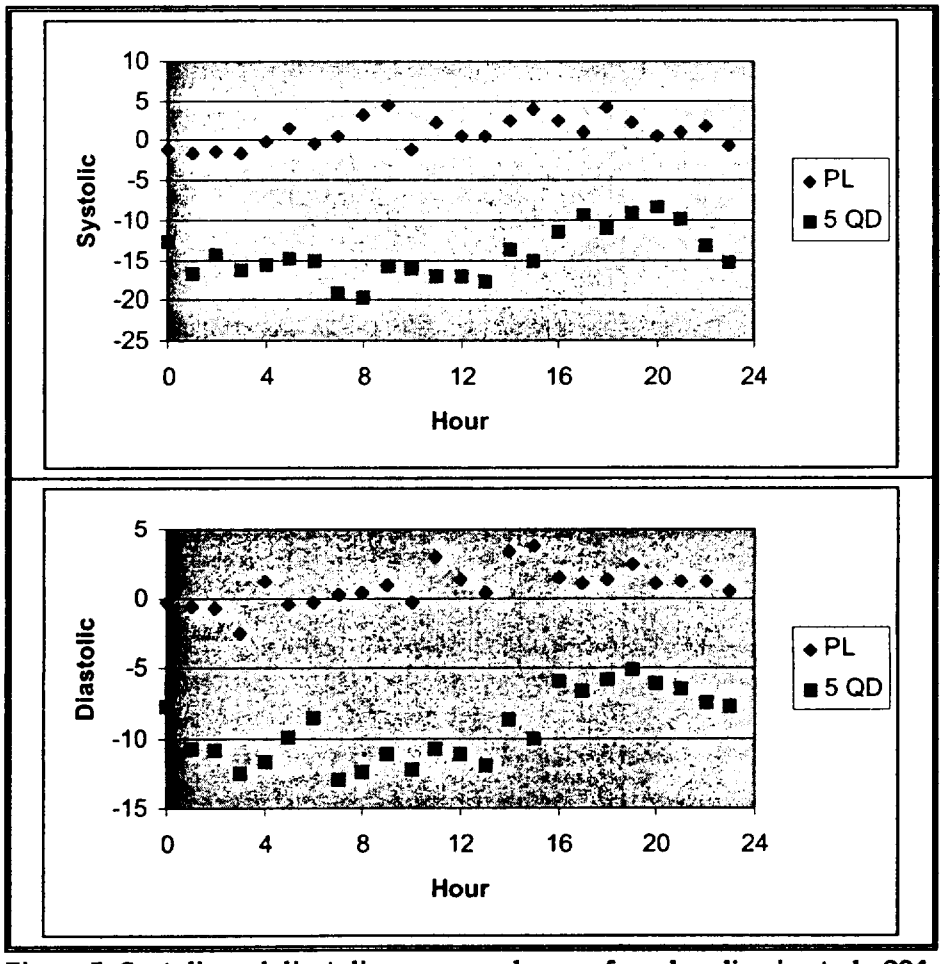

Figure 5. Systolic and diastolic pressure changes from baseline in study 204.

Data are shown for the placebo and once-daily 5-mg doses. The amount of variation in the placebo group is similar to the amount of variation in the 5-mg dose.

Thus, the flatness of the once-daily treatment effect does not appear to be the result of the high dose completely saturating receptors throughout the interdosing interval.

Classically, decisions about once- and twice-daily dosing have considered cuff blood pressure assessments at (estimated) peak and the interdosing interval. These data are available for study 10, a 12-week, parallel, placebo-controlled study of doses 5, 10, and 20 mg, as shown in Table 1.

Table 1. Trough-peak diastolic pressures in Study 10[1].

		Dose (mg)		
		5	**10**	**20**
Trough	Change from baseline	15.4	16.0	17.7
	Placebo	11.9	11.9	11.9
	Double difference	3.5	4.1	5.8
Peak	Change from baseline	16.4	16.7	18.6
	Placebo	11.4	11.4	11.4
	Double difference	5.0	5.3	7.2
Trough-peak ratio		0.70	0.77	0.81

Thus, cuff trough-peak ratios are also most compatible with once-daily dosing.

Alternatively, one can consider the absolute difference between trough and peak, which amounts to about 1.5 mmHg (diastolic), not all of which can be expected at trough with twice-daily dosing.

One can expect to get some return on twice-daily dosing, and even more with dosing three or four times per day, but the amount of return on twice-daily dosing is already a poor investment.

[1] *These numbers differ from the primary medical review, which repeats the error in the sponsor's study report, basing the trough-peak ratio on the changes from baseline, without subtracting the placebo effect.*

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/s/

Norman Stockbridge
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MEDICAL OFFICER

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Secondary Review

NDA: 21-286

Sponsor: Sankyo Pharma

Submission: Original NDA for olmesartan medoxomil (Benicar™; CS-866), a new molecular entity for once-daily administration in the treatment of mild-to-moderate essential hypertension.

Review date: 4 October 2001

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Summary: Olmesartan appears to be an effective treatment for mild-to-moderate hypertension. There is a lingering question about its carcinogenic potential.

Distribution: NDA 21-286

HFD-110/Project Manager

HFD-110/Stockbridge

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1 Background

Olmesartan medoxomil was developed under IND [redacted] opened 1 May 1995. NDA 21-286 was received 26 July 2000. The 12-month action goal date is 25 July 2001.

Inspections of several clinical sites were undertaken by DSI, despite the Division's recommendations. There were no problems that would alter the interpretation of the sponsor's clinical studies.

Inspections of manufacturing sites have been performed and the results deemed acceptable as of 24 May 2001.

The sponsor has provided a financial disclosure statement, denying inappropriate financial arrangements as defined under 21 CFR 54.2(a), (b), or (f).

Olmesartan has not been marketed in other countries.

Pediatric studies have not been performed.

This review is based upon the following documents: review of chemistry, manufacturing, and controls (Dr. Zielinski), dated 20 April 2001; draft review of pharmacology and toxicology (Dr. Jagadeesh), dated 31 May 2001; meeting minutes for the Executive CAC, dated 22 March 2001, meeting minutes for the full CAC, dated 19 June 2001, clinical pharmacology and biopharmaceutics reviews (Drs. Al-Habet, Fadiran, and Robbie), dated 14 November 2000, 27 March 2001, and 7 May 2001; statistical review (Dr. Hung), dated 17 March 2001, and the medical review (Drs. Rodin, Targum, and Williams), dated 2 July 2001.

2 Chemistry

There are no asymmetric carbons in the structure of olmesartan.

Dr. Zielinski's review describes olmesartan 5, [redacted] 20, and 40-mg film-coated tablets. However, apparently, the sponsor intends to market only the 20- and 40-mg tablets.

The proposed trade name (Benicar) is acceptable. The nonproprietary name, olmesartan medoxomil, is accepable.

Establishment inspections are pending.

Stability data support a 24-month expiration date.

Various minor deficiencies are identified; none render the application non-approvable.

3 Pharmacology

3.1 Mechanism

Olmesartan medoxomil is an orally absorbable pro-drug for olmesartan. Both are angiotensin II receptor non-competitive antagonists, with olmesartan having a 4-fold lower IC_{50}. Olmesartan's IC_{50} is about 10-fold lower than that for losartan and about the same as for candesartan, and it is highly selective for the adrenocortical (AT_1) receptor. Antagonism of angiotensin pressor effects was demonstrated in several species. Dose-related antihypertensive effects were demonstrated in various renin-dependent models of hypertension.

3.2 Absorption, metabolism, excretion

When administered by oral or IV routes, olmesartan medoxomil is excreted 10% in the urine and 90% in feces, mostly as free olmesartan, and the rest olmesartan glucuronide. Circulating olmesartan is highly bound to plasma proteins.

3.3 Toxicity

Acute oral toxicity is very low; LD_{50} was >2 g/kg in mice, rats, and dogs.

During chronic administration in rats, there were dose-related effects in the kidney: thickening of the artery wall, tubular cell hyperplasia, and JGA hypertrophy. Renal changes were accompanied by BUN increase in chronically dosed dogs.

3.4 Carcinogenicity

Carcinogenicity studies in rats (2 years) and transgenic mice (6 months) demonstrated mortality similar in control and groups dosed up to 2 g/kg/day (a dose producing peak plasma concentrations about 8-fold higher than seen in humans with a 40-mg dose). Tumorogenicity findings were similar in all treatment groups.

3.5 Clastogenicity, mutagenicity

Olmesartan medoxomil was negative in the Ames reverse mutagenicity assay. A second bacterial gene mutation assay was also negative. A bacterial gene mutation assay utilizing the ester side chain of olmesartan medoxomil was positive, as was a similar assay of diacetyl, a metabolic product of the ester side chain.

Break and exchange type abnormalities were demonstrated in two chromosomal aberration tests of olmesartan medoxomil in Chinese hamster lung fibroblasts. The tests characterized olmesartan medoxomil to be a "middle grade" mutagen. Similar tests found olmesartan and the diacetyl metabolite of the side chain, but not the ester side chain, also to be clastogenic.

Olmesartan medoxomil was mutagenic in a mouse lymphoma cell assay. This result was confirmed in a repeat comparison with (less positive) losartan. Olmesartan medoxomil was also mutagenic in an in vivo gene mutation assay of the mouse intestinal mucosa.

Olmesartan medoxomil and olmesartan were negative in Syrian hamster embryo cell transformation assays. Olmesartan medoxomil was negative in an in vivo assay of unscheduled DNA synthesis in the rat liver, and it was not clastogenic in two mouse micronucleus tests.

Plausibly, the chromosomal aberrations and mutagenic potential of olmesartan medoxomil in vitro are attributable to in vitro liberation of diacetyl, which, despite similar results in the literature, is "generally regarded as safe". The amount of diacetyl associated with the highest proposed dose of olmesartan is less than the average dietary content. Plausible as it may be, the sponsor's studies do not demonstrate the clastogenicity and mutagenicity safety of olmesartan medoxomil, and cross-NDA

comparisons with other angiotensin II receptor antagonists do not bear out the sponsor's contention that the positive findings are a class effect.

3.6 Reproductive toxicology

There was no significant effect of olmesartan medoxomil in a rat fertility and early gestational (Segment I) assay, at doses up to 1 g/kg/day. In Segment II developmental toxicity studies in rats, the no observed effect level was 200 mg/kg/day in one study, but this dose affected fetal growth in a second study. There was no embryo-fetal toxicity demonstrated in a Segment II study in the rabbit. In two late gestation and lactation (Segment III) studies in the rat, there was no effect of olmesartan medoxomil on reproductive capacity in maternal and F_1 offspring, but renal pelvic dilation was prominent in the F_1 generation animals receiving >0.3 mg/kg/day. Olmesartan appears in milk of rats administered olmesartan medoxomil.

3.7 CAC assessment and recommendations

The Executive CAC expressed concern over renal tubular hyperplasia and mesotheliomas in the 2-year study in rats. The Division was asked to review the incidence of hyperplasia in all organs where there was a nominal increase in tumor incidence. Where there appeared to be increases in both, the sponsor was asked to provide historical control data. The sponsor was also to be asked for historical data on mesothelioma, uterine endometrial stromal polyps, uterine endometrial stromal sarcomas, renal tubular adenomas, and renal tubular carcinomas.

The full CAC was advised that the incidence of renal tubular cell neoplasia exceeds the sponsor's control rate. The sponsor argued that tubular cell hyperplasia was slight, and lacked mitoses or cell atypia. These difficulties of interpretation led to the proposal of a blinded, third-party assessment of the source histological material. The CAC formally voted that the available data were positive for the rat tubular findings and that these findings were relevant to man. A non-GLP study in rats (Hras2 assay) was considered negative and worthy of description in the label.

3.8 Renal tumors

Serial sectioning and blinded reading of the rat kidneys from the 2-year carcinogenicity study widened the tumor incidence gap between placebo and olmesartan-treated groups. However, there are still too few events to expect a dose-response relationship.

The accumulated findings from 2-year carcinogenicity studies for other angiotensin receptor antagonists suggests that this is a class effect with only random variation among the members. Olmesartan may be the worst of the class or it may really be no different. There are evident differences among readers, and many of the carcinogenicity studies are evaluated unblinded to treatment group.

The relationship between the tumor findings in rats and the risk of carcinogenicity in man is completely unknown.

Were olmesartan medoxomil to be approved, the pharmacology review includes comments for the label.

4 Biopharmaceutics

Olmesartan medoxomil is about 26% orally bioavailable. Bioavailability is not affected by food. Olmesartan medoxomil is rapidly and completely metabolized to olmesartan. There is very little subsequent metabolism.

Peak plasma concentrations of olmesartan occur after 1-2 hours, and terminal elimination has a half-life of about 13 hours. With once-daily dosing, plasma levels are proportional to dose up to 80 mg, and steady state is reached with little accumulation after a few days.

Olmesartan is highly bound to plasma proteins, up to levels well above those produced by proposed doses.

Olmesartan is mostly excreted in the feces. Nevertheless, renal impairment characterized by creatinine clearance <20 mL/min results in a 3-fold increase in AUC. Moderate hepatic impairment (Childs-Pugh score 7-9) results in less than 2-fold increase in AUC and Cmax.

Formal drug interaction studies were performed with digoxin, warfarin, and antacids; there were no clinically significant effects. Olmesartan appears to be not a substrate for P450 enzymes, nor is it an inhibitor or an inducer.

There is no apparent effect of gender on the pharmacokinetics for olmesartan medoxomil. Elderly subjects have AUC less than 50% higher than young subjects receiving the same dose, a difference unlikely to merit age-related dose adjustment.

Angiotensin I, angiotensin II, and plasma renin activity increase during dosing with olmesartan.

There appear to be no data from which to assess the relationships among plasma levels of olmesartan, time, and effects on blood pressure.

Tablets containing olmesartan medoxomil 5, 20, and 40 mg were developed. Dissolution profiles for these were sufficiently similar in three media that OPB waived the requirement for a bioequivalence study of the 5- and 40-mg tablets. The research and to-be-marketed formulations were judged to be bioequivalent.

5 Effectiveness

There are numerous adequate, parallel placebo-controlled, fixed-dose studies from which to conclude that olmesartan is effective in reducing the blood pressure of subjects with mild-to-moderate essential hypertension. An estimate of the shape of the dose-response relationship can be discerned from Figure 1.

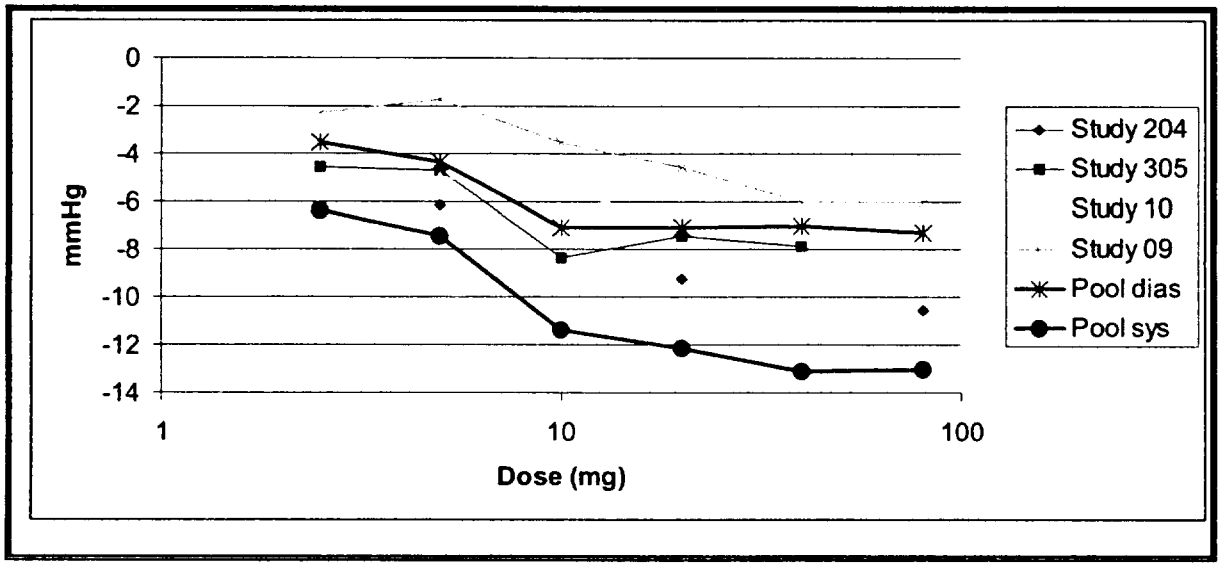

Figure 1. Dose-response for olmesartan medoxomil.

Results are shown for baseline- and placebo-subtracted sitting diastolic and systolic pressures. Results are shown for selected studies (diastolic pressure only). Other parallel studies are included in the sponsor's pooled analyses of diastolic and systolic pressures. Pooled analyses include studies of 6-12 weeks.

Dose-related changes in systolic pressure were greater than those for diastolic pressure. Doses >40 mg are probably not much more effective. The lowest dose studied (2.5 mg) has about half of the maximum obtainable effect.

The sponsor did several ABPM studies[1], useful for assessing the appropriate interdosing interval. Baseline- and placebo-subtracted hourly averages of diastolic pressure are shown in Figure 2 (Study 204).

[1] *The sponsor and medical and statistical reviewers have extensively described results of these studies for 24-hour mean effects and daytime and nighttime mean effects. However, such analyses should not be made the basis for decision-making, since they do not show that a treatment is effective throughout the interdosing interval.*

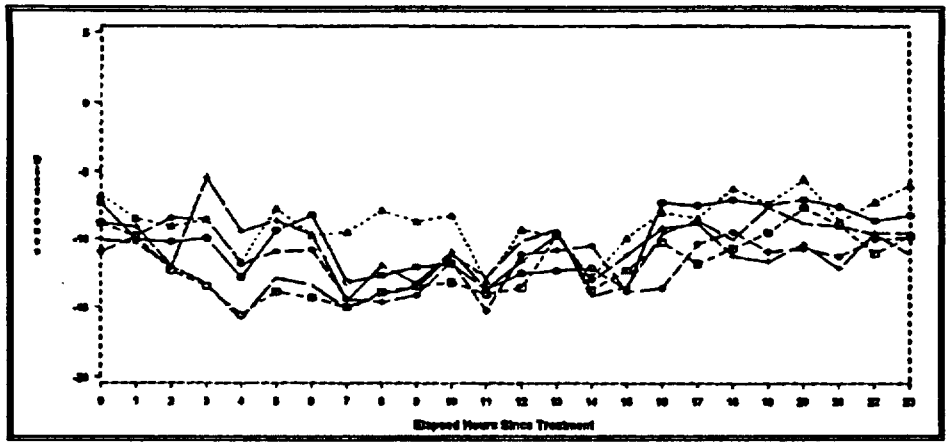

Figure 2. Baseline- and placebo-subtracted effects on diastolic pressure (Study 204).

Curves are hourly average ABPM for doses of 5, 20, and 80 mg qd, and 2.5, 5, and 40 mg bid.

Plainly, even without seeing which curve is which, they are all effective, and the treatment effects wane little over the interdosing intervals of 12 or 24 hours. There is no benefit to twice-daily dosing.

The primary medical review shows figures of baseline-subtracted diastolic pressure changes as a function of time (pooled studies). From these, the baseline- and placebo-subtracted diastolic changes as a function of time were estimated, as shown in Figure 3.

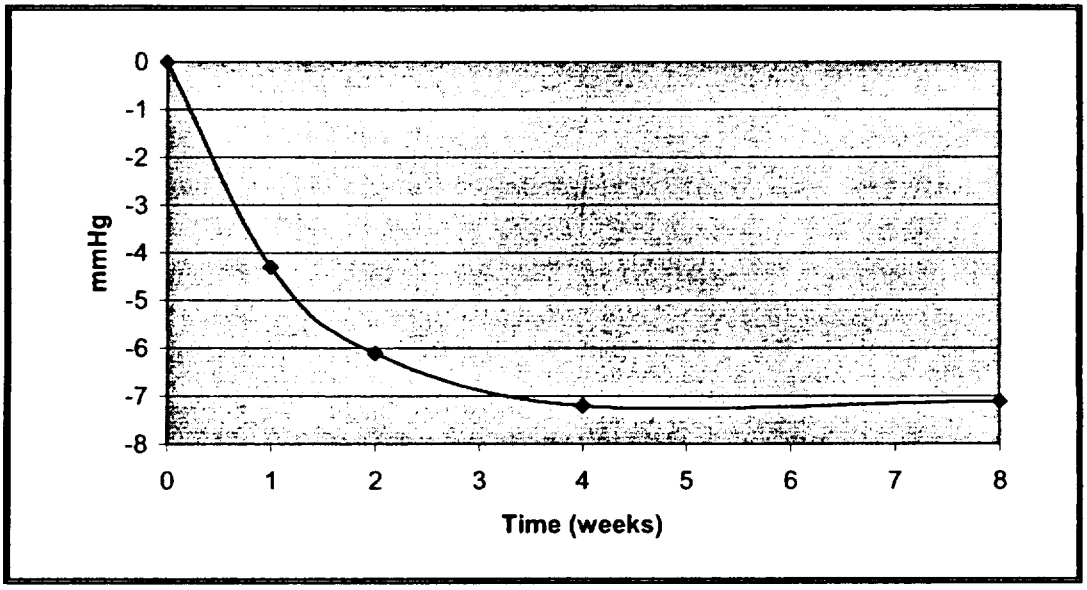

Figure 3. Time course of treatment effect with once-daily dosing.

The figure shows the baseline- and placebo-subtracted estimates of the sitting diastolic pressures in pooled studies of the 80-mg dose.

These results show that much of the treatment effect has developed after 2 weeks of once-daily dosing. This, then, is a reasonable minimum interval for titration steps.

There appear to be no placebo-withdrawal studies after long-term treatment. However, there is a washout after a one-year open-label study demonstrating the expected return to near baseline blood pressure levels, which is better data than one often sees.

The sponsor's analyses of subgroups is suggestive of no clinically significant effect of sex, and a somewhat smaller effect in the elderly. As with other renin system antagonists, treatment with olmesartan alone is less effective in Blacks; the same may be true of Hispanics.

6 Safety

The safety analysis comes from more than 3000 subjects, over 2000 from active treatment arms of parallel, placebo-controlled studies, representing about 1500 subject-years of exposure. More than 500 subjects received olmesartan for more than one year in open-label follow-on studies. A minor fraction of the total exposure (and no long-term data) came from subjects receiving 80 mg. For doses up to 40 mg, this represents a safety database similar to that of most modern era new molecular entities for the treatment of hypertension. The scope of the data obtained was also conventional.

There were two deaths within 30 days of the last dose of olmesartan. One was attributed to esophageal cancer and one was accidental. In neither is study drug a likely contributing factor.

Serious adverse events were very rare on olmesartan or placebo in controlled studies, with no event statistically likely to have been treatment-related. In long-term open-label studies, the most common serious adverse events were chest pain (4 subjects) and angina (3 subjects); neither these nor the more rarely observed events being uncommon in the studied population.

A total of 1.6% of subjects in placebo-controlled studies discontinued for adverse events. The only adverse events leading to discontinuation of olmesartan in >0.1% of subjects in placebo-controlled studies were dizziness (0.2%) and angina (0.2%). In all studies of hypertensive subjects, the only adverse event leading to discontinuation of >0.2% of olmesartan subjects was dizziness (0.3%).

The most common adverse events in placebo-controlled studies, with an incidence of at least 1% on olmesartan and more common on olmesartan than on placebo, are shown in Table 1.

Table 1. Incidence (%) of adverse events more common on olmesartan than placebo.

	Placebo N=555	Olmes N=2540		Placebo N=555	Olmes N=2540
Flu-like symptoms	2.9	3.1	CPK increased	1.1	1.6
Dizziness	0.9	2.8	Injury	1.3	1.3
Bronchitis	1.8	2.0	Hypertriglyceridemia	1.1	1.1
Hematuria	1.8	2.0	Diarrhea	0.7	1.1
Back pain	1.4	1.6			

Of these, the highest ratios of incidence on olmesartan to incidence on placebo are for dizziness and CPK elevation.

Among assessments of clinical chemistry, there is the faintest evidence of an effect of olmesartan on hepatic enzyme levels. In placebo controlled studies, the incidence of subjects going from within normal limits to >2 times upper limit of normal is shown in Table 2.

Table 2. Treatment-emergent elevations in hepatic enzymes in placebo-controlled studies.

	Placebo N=236-278	Olmesartan N=1168-1304
SGOT	0.2%	0.7%
SGPT	0.6%	1.1%
GGT	0.2%	2.2%

However, the incidence of discontinuations for elevated enzymes was low and greater on placebo than on olmesartan in controlled studies. Also the incidence of values of SGOT

or SGPT >3 times upper limit of normal was also higher on placebo than on olmesartan. Thus, there may be a real effect of olmesartan on hepatic enzyme levels, but there is little to suggest a safety concern. This description and assessment are similar to those in the labels of losartan and candesartan.

As noted above, CPK elevations considered adverse events were more common on olmesartan than on placebo. Overall, the incidence of a marked abnormality in CPK (>1000 U/L) was 0.4% on placebo and 1.0% on olmesartan. Most elevations in CPK came in subjects nominally abnormal at baseline and most were transient, resolving while subjects remained on study drug. Most elevations were attributed by the investigator to physical activity. CPK elevation was listed as a contributing factor for discontinuation of one subject.

Olmesartan has no clinically significant effect on heart rate or ECG parameters.

Olmesartan was used safely with HCTZ and usual concomitant medications.

7 Summary and recommendation

Olmesartan medoxomil is clearly effective as a once-daily antihypertensive. Adequate instructions for use can be written. Safety data, obtained in a conventionally sized, conventionally monitored development program, make olmesartan look like other members of the angiotensin II receptor antagonist family.

A better choice of doses would be 2.5 or 10 and 40 mg, with the lower dose the starting dose in everyone.

Clastogenicity and mutagenicity data and possible findings of renal tubular hyperplasia and tumor incidence in the 2-year rat carcinogenicity study together are plausibly real findings that most likely do not distinguish olmesartan medoxomil from other members of the angiotensin receptor blocker class.

There are few cases of renal tumors in man in association with other angiotensin receptor antagonists, but the short length of exposure and the low sensitivity of post-marketing safety monitoring limit the value of these data. Thus, the clinical significance of the findings of the carcinogenicity related to this or other angiotensin receptor antagonists is unknown, and the only issue is what needs to be known prior to approval.

There is a pretty good argument that olmesartan medoxomil is not demonstrably different from other members of its class, so it should share the claim for use in mild-to-moderate hypertension, as long as any of them do.

The following areas need to be addressed in the label: (1) dose-response graph should show placebo-subtracted data for all doses assessed, and (2) twice-daily use should be discouraged as not useful.

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/s/

Norman Stockbridge
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MEDICAL OFFICER

Shari L. Targum, M.D.
Division of Cardio-Renal Drug Products, HFD-110

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Memorandum

DATE: February 22, 2002

FROM: Shari L. Targum, M.D.
TO: NDA 21-286 Benicar™ (olmesartan medoxomil) Tablets

SUBJECT: Safety Update
SPONSOR: Sankyo Pharma, Inc
DATE OF SUBMISSION: January 7, 2002
DATE RECEIVED: January 9, 2002

Indication: Hypertension
Dosage: 5,—20, 40 mg tablets

This safety update will focus on clinical data. For further discussion of nonclinical pharmacology and toxicology and preclinical studies, please see the review by the assigned pharmacologist.
This submission covers the period of August 2, 2000 to July 31, 2001. Included in this submission were four clinical study reports, 92 serious adverse events, and 13 publications containing clinical data.
In this review, CS-866 and olmesartan will be used interchangeably; both refer to the product Benicar™.

Table 1. Clinical studies completed from August 2, 2000 to July 31, 2001

Study number	Title	N (safety analysis)	Primary objective
SE-866/10-01 (Final analysis—1 year)	A Multi-Centre Double-Blind Long-term, Safety, Efficacy and Tolerability Study of the Oral Angiotensin II-Antagonist CS-866 in Patients with Mild to Moderate Essential Hypertension (Prolongation of Study SE-866/10)	459	Long-term safety and tolerability
SE-866/10-01 (Final analysis—2 year)	See above (combined data of studies SE-866/10 and SE-866 10-01)	462	Long-term safety and tolerability
SE-866/24	The Effect of the Combination of the Oral Angiotensin II-Antagonist CS-866 and Pravastatin on Pharmacokinetics, Safety, and Tolerability in Healthy, Male Subjects	24	Compare plasma steady-state pharmacokinetic parameters of olmesartan alone, pravastatin alone, and both drugs coadministered.
SE-866CMB/01	Effect of the Combination of the Oral Angiotensin II Antagonist CS-866 and Hydrochlorothiazide on Pharmacokinetics, Safety and Tolerability in Healthy, Male Subjects	23	Effect of olmesartan on plasma pK parameters of HCTZ and effect of HCTZ on plasma pK parameters of RNH-6270

1.0 Study Synopses:
For study results please see the Individual Study Reports

1.1. Study SE-866/10-01(Please see original review for additional discussion of SE-866/10):
This was a randomized, double-blind, placebo-controlled long-term study at 42 sites in Germany and Poland. Responders completing SE-866/10 (ie, DBP $\leq$ 90 mm Hg) were asked to undergo a 2-week single-blind placebo

period followed by 52 weeks of double-blind therapy (CS-866 5 mg, 10 mg, 20 mg, placebo, or CS-866 + HCTZ) at the same dose as in the preceding study. A total of 462 patients were screened and 459 patients were randomized to active treatment. Efficacy measurements included: change in trough sitting DBP from baseline to Week 52, change in trough DBP, SBP, PR from baseline to Weeks 2, 6, 16, 28, 40, and 52, probability of treatment failure at the same time points, need for supplemental HCTZ, and difference in mean sitting trough DBP over the 2 week placebo period between study SE-866/10 and SE-866/10-01.

1.2. A Final Analysis was done of the 2-year combined evaluation of studies SE-866/10 and SE-866/10-01.

1.3. Study SE-866/24: This was a randomized, open-label, single-center, 3-way crossover study conducted in Germany. The subject population was healthy male volunteers. The primary objective was to compare plasma steady state pharmacokinetics of CS-866 alone, pravastatin alone, and both drugs coadministered. Secondary objectives were to evaluate urinary pK for RNH-6270 after multiple dosing, and to investigate safety/tolerability of the different treatments.
A total of 24 subjects were enrolled and completed all treatment periods.

1.4 Study SE-866 CMB/01: This was a randomized, open-label, single-center, 3-way crossover study in Germany. The primary objective was to assess the influence of CS-866 on HCTZ pharmacokinetics and the influence of HCTZ on RNH-6270 pharmacokinetics at steady state. Secondary objectives were to evaluate pharmacokinetics of RNH-6270 and HCTZ in urine and to assess safety/tolerability of the different treatments.
A total of 24 subjects were enrolled; 1 subject was withdrawn due to a fractured nasal bone and 23 subjects completed the study. Each subject received, in random order, CS-866 20 mg (treatment A), HCTZ 25 mg (treatment B), and CS-866 20 mg with HCTZ 25 mg (treatment C).

2.0 Safety Update:

2.1. Deaths:
From the table of serious adverse events, seven patients developed fatal adverse events. Narratives are presented below. The event rate appears to be small and not increased in the CS-866 (or blinded) group.

Table 2. Deaths by Study Number and Patient (August 2, 2000-July 31, 2001)

Study Number/site #	Patient R/S number	Preferred term (reported term)	Drug	Outcome	Drug status
318/014	NA/70308	Death	Placebo run-in	Fatal	N/A
318/013	NA/70460	Ruptured aneurysm (cerebral), pulmonary edema, respiratory failure	Placebo run-in	Fatal	N/A
420/101	NA/200869	Cardiac arrest	Placebo run-in	Fatal	Withdrawn
SE-010-01/066	0793/100711	Inflicted injury (fractured femur), intestinal ischemia	Placebo	Fatal	Withdrawn
SE-CMB-002/052	1935/22901	Cerebellar hemorrhage	Blinded	Fatal	Withdrawn
SE-CMB-002/094	1251/CMB02 1874	Sudden death	Blinded	Fatal	Withdrawn
SE-CMB-002/102	1622/CMB02 2377	Hemorrhagic stroke	CS-866 20 mg + HCTZ 25 mg QD	Fatal	Withdrawn

2.1.1. Narratives: Fatal Adverse Events:

1. Patient #S70308 was a 57 year old Black female screened for study 866-318 on June 8, 2000. She was asymptomatic, with an unremarkable physical exam and LVH voltage on EKG. On June 16, 2000 she began placebo run-in. On July 10, 2000, while on placebo, she was found unconscious in her bathroom; resuscitation in the ER was unsuccessful (in retrospect, she reported weakness and fatigue 2 days prior to the event). The cause of death was (per autopsy) ruptured aorta with dissection and pericardial tamponade.

2. Patient #S70460 was a 47 year old White female hypertensive who received placebo from September 6, 2000 through October 5, 2000 during the placebo run-in; the patient failed to qualify for randomization and was discontinued. On November 21, 2000 the patient suddenly lost consciousness, became dyspneic, and was intubated due to pulmonary edema. CT scan showed subarachnoid hemorrhage, the patient became comatose with brain death established on November 26, 2000.
3. Patient #S200869 was a 53 year old Black male who enrolled in 866-420 on June 25, 2001 and began placebo run-in on July 2, 2001. No complaints were noted during visits on July 9, 2001 (BP 16-164/94-96 mm Hg) and July 17, 2001 (168-172/100 mm Hg). On July 17, 2001 the site was notified that the patient was brought to a local ER in full cardiac arrest; he died later that day.
4. Patient # S22901/1935 was a 64 year old White female who enrolled in SE-866 CMB/02, received placebo August 20, 2000-September 19, 2000, and received randomized study drug (either CS-866 or placebo and HCTZ) from September 20-26, 2000. On September 26, 2000 she developed headache, nausea, near-syncope with BP 240/130 mm Hg; she received 15 mg nifedipine with some lowering of BP, and was hospitalized with a left cerebellar bleed with brain stem compression. Subsequent course was complicated by ileus due to C. difficile enterocolitis resulting in shock and renal insufficiency. On November 2, 2000 she developed circulatory collapse and high fever, became anuric and died on November 5, 2000.
5. Patient # SCMB021874/1251 was a 22 year old White male who enrolled in SE-866 CMB/02 and began randomized medication (CS-866 or HCTZ or placebo) on October 24, 2000. On January 1, 2001 he was found dead in bed. He had taken bisoprolol for HTN prior to September 19, 2000. An EKG on August 18, 2000 showed LVH. (Reviewer: Unclear as to previous workup for secondary HTN in this 22 year old).
6. Patient #CMB022377/1622 was a 56 year old White male who enrolled in SE-866 CMB/02 and received CS-866 20 mg QD and HCTZ 25 mg QD from March 7, 2001-July 3, 2001. On July 3, 2001 he didn't "feel well" and an EKG revealed RBBB and inferior ischemia; BP was 220/120 mm Hg. He was hospitalized, treated with furosemide, lost consciousness (BP 200-220/100 mm Hg), underwent craniotomy with evacuation of hematoma and decompression of the brain stem/bulb. He died on July 7, 2001.
7. Patient #S100711/0793 was a 90 year old White male, randomized to placebo July 22,1999 to January 27, 2000. The patient fell, sustained a fractured femur and underwent osteosynthesis with traction screw and condyle disk. On February 12, 2000 he developed ischemic colitis, did not recover, and died on February 16, 2000.

2.2. Serious Adverse Events: In addition to the deaths, there were 92 serious adverse events (including 3 submitted as expedited review) during the reporting time period. Of the 89 SAE narratives, 56 were reported as occurring under blinded therapy; another 21 cases occurred on placebo or during screening. No unusual trends in serious adverse events were identified by the reviewer; however, more definitive conclusions await unblinding of therapy.

2. 3. Literature Review:
The clinical studies and review articles in this submission were reviewed. No new or unusual safety issues were identified. In addition, this reviewer conducted a separate literature search (via Pubmed) and did not identify any new safety concerns.

2.4. Reviewer Conclusions: Safety Update:
1. No unusual trends in deaths or serious adverse events were identified.
2. Over 50% of the SAE narratives occurred with therapy still blinded; definitive safety conclusions await unblinding of therapy.
3. Olmesartan appears to be well-tolerated.
4. Treatment-emergent AE in the combined analysis (Section 3.2, below) of SE-866/10 and SE-866/10-01 appear consistent with the draft labeling proposed by the Agency.

3.0. Individual Study Reports:
3.1. SE-866/10-01:
Title: A Multicentre, Double-Blind, Long Term Safety, Tolerability and Efficacy Study of the Oral Angiotensin II-Antagonist CS-866 in Patients with Mild to Moderate Essential Hypertension (Prolongation of Study SE-866/10)

Please see the Medical Officer review of the original submission for a description of SE-866/10 and SE-866/10-01.

Included in this Safety Update was a final study report of a 52-week long-term extension of SE-866/10 (a one-year study). The primary objective of this trial was assessment of long term safety and tolerability (via AEs, BP/HR, laboratory tests and ECG recordings. Secondary objectives included: effects on BP lowering and pulse at trough after an additional 2, 6, 16, 28, 40 and 52 weeks of treatment; failure rate of CS-866; effect of age on efficacy, safety and tolerability.

After completing SE-866/10, responders (mean sitting DBP $\leq$ 90 mm Hg) had the option of continuing treatment for another year (two weeks placebo plus another 52 weeks of their same dose of double-blind trial medication—CS-866 5, 10 or 20 mg QD or placebo). Those patients who received add-on HCTZ in the previous study were to maintain the same dose of HCTZ plus double-blind medication. If BP was uncontrolled (DBP > 90 mm Hg) on monotherapy, then HCTZ was added (either 12.5 mg or 25 mg QD). If the BP remained uncontrolled on HCTZ 25 mg QD plus trial medication, then the patient was withdrawn from the study. Safety parameters included routine laboratory testing, EKGs, and adverse event monitoring. Any patient with an AE at the final examination or an unknown outcome was asked to return for a safety follow-up visit up to 4 weeks after the last dose of trial medication.

The safety analysis set consisted of all patients who took trial medication at least once. The full analysis set included all patients of the safety set for whom data were available (with LOCF approach). The primary safety variable was the rate of treatment-emergent AE occurrences.

A total of 462 patients were screened at 42 centers. Three patients dropped out during the placebo run-in phase and 459 patients entered active treatment; 409 completed the study. Sixteen patients dropped out due to adverse events, 1 due to lack of efficacy, 11 withdrew consent, 2 due to concomitant medications, and 20 for other reasons.

Table 3. Patient Disposition (SE-866/10-01)*

	Placebo	5 mg QD	10 mg QD	20 mg QD
Entering	50	136	133	133
Completing	42	124	122	121
Full analysis set	50	136	133	133
Safety set	52	136	135	136
Valid cases set	35	111	106	105

*Note: unequal randomization scheme (2:2:2:1 per Study SE-866/10).

Demographic data: All patients were Caucasian. Median age was 59-61 years. There was a higher percentage of males in the CS-866 5 mg group, and a lower percentage of patients pretreated with HCTZ in the CS-866 20 mg group. Otherwise there appeared to be no imbalance between treatment groups.

Exposure: Mean exposure ranged from 321 days for placebo to 353 days for the CS-866 5 mg group. Mean exposure to HCTZ ranged from 72 days (CS-866 20 mg group) to 171 days (placebo).

Results:

Safety/Tolerability: During the active treatment period, about 59-65% of patients developed treatment-emergent adverse events. Most common treatment-emergent adverse events in >5% of patients on CS-866 (and occurring more frequently on drug compared to placebo) were: back pain, influenza-like symptoms, gastroenteritis, and bronchitis. Treatment-emergent AEs related to elevated liver enzymes were reported in 13 CS-866 patients (4 in the 5 mg group, 4 in the 10 mg group, and 5 in the 20 mg group). Serious AEs were noted in 19 patients during active treatment and safety follow-up. Four deaths were reported (2 in placebo; 1 in placebo/HCTZ; 1 in CS-866 5 mg group).

Table 4. Deaths: SE-866/10-01

Patient run-in/random. #	Event	Treatment	Onset day after 1st treatment
100094/0066	Sudden death	Placebo/HCTZ 25 mg	150
100847/0427	Cerebrovascular disorder	CS-866 5 mg	263
100953/0505	MI/sudden death	Placebo	213
100711/0793*	Inflicted injury/intestinal ischemia	Placebo	221/238

*This patient is also represented in Table 2.

Table 5. Serious AE: SE-866/10-01 (excluding deaths)

Patient run-in/random. #	Event	Treatment	Onset day after 1st treatment	Outcome
100237/0167	Cholangitis/cholelithiasis	CS-866 10 mg	25	Recovered
100321/0226	Bronchitis/hypertension aggravated/left CHF	CS-866 20 mg/HCTZ 12.5 mg	15/16	Recovered
100041/0029	Arrhythmia	Placebo	87	Recovered w/sequelae
100233/0162	GI malignancy	Placebo/125 mg HCTZ	143	Not recovered
100256/0181	Angina pectoris	CS-866 5 mg	29	Recovered
100334/0237	Mesothelioma	Placebo	64	Not recovered
100252/0177	Inflicted injury	CS-866 20 mg	165	Recovered
100312/0219	Surgical intervention	CS-866 20 mg	120	Recovered
100317/0224	Surgical intervention	CS-866 20 mg	15	Recovered
100012/0009	Myocardial infarction	CS-866 5 mg	288	Recovered
100558/0605	Syncope	CS-866 5 mg/12.5 mg HCTZ	186	Recovered
100303/0215	Neurosis	CS-866 20 mg	126	Recovered
100266/0188	DVT; gastric CA	CS-866 10 mg	39;31	Recovered; recovered w/sequelae
100384/0626	Genital ulcer	Placebo	86	Recovered
100946/0531	AV block	CS-866 5 mg	336	Recovered w/sequelae

Withdrawals due to AE: Fourteen patients were withdrawn from this trial due to SAE and two patients were dropped due to treatment-emergent adverse events (one was withdrawn because of hyperglycemia; the other developed increased GGTP values).

Treatment-emergent AEs related to liver enzyme elevation occurred in 13 patients; in 7 of these patients, the liver enzymes normalized by Week 52. In another 4 patients, Week 52 liver enzymes were unchanged or lower than values at Week 0.

Please see the combined analysis for a discussion of treatment-emergent AE.

Efficacy:

Table 6 presents efficacy results for sitting SBP and DBP. If the full analysis set is used, then the differences from placebo are not statistically significant. If the valid set is used, then statistically significant differences from placebo are seen in the CS-866 20 mg group (sitting DBP). No clinically relevant changes in heart rate were seen in the CS-866 group.

Table 6. Change in mean sitting trough DBP and SBP from baseline to Visit 8/Week 52 (full analysis set)

	CS-866 5 mg (N=136)	CS-866 10 mg (N=133)	CS-866 20 mg (N=133)	Placebo (N=50)
Trough mean sitting DBP (mm Hg)				
LS Means change from baseline	-20.7	-20.0	-21.3	-20.3

p-value* of the differences from baseline	0.0001	0.0001	0.0001	0.0001
Difference from placebo (95% CI)	-0.9 (-3.0, 1.2)	-0.2 (-2.3, 1.8)	-1.8 (-3.8, 0.3)	--
Trough mean sitting SBP (mm Hg)				
LS Means change from baseline	-24.6	-23.6	-25	-22.1
Difference from placebo (95% CI)	-2.7 (-7.6, 2.2)	-2.0 (-6.9, 2.9)	-4.1 (-9, 0.9)	--

*p-value based on ANOVA and Dunnett's Many-to-One procedure

Table 7 shows the number and percent of patients requiring additional HCTZ treatment. The sponsor has presented this table to show that a higher percentage of patients on placebo and low-dose olmesartan required additional HCTZ therapy than those on high-dose olmesartan. This reviewer notes that the numbers of patients on placebo as well as HCTZ are relatively small; thus, small changes in the placebo group are reflected in greater percentage changes.

Table 7. Additional HCTZ treatment (full analysis set LOCF)

HCTZ N (%)	CS-866 5 mg (N=136)	CS-866 10 mg (N=133)	CS-866 20 mg (N=133)	Placebo (N=50)
Visit 3/Week 2				
0 mg	91 (67)	92 (70)	107 (81)	26 (52)
12.5 mg	26 (19)	24 (18)	20 (15)	11 (22)
25 mg	19 (14)	17 (13)	6 (5)	13 (26)
Visit 8/Week 52				
0 mg	86 (63)	88(66)	105 (79)	23 (46)
12.5 mg	28 (21)	25 (19)	19 (14)	11 (22)
25 mg	22 (16)	20 (15)	9 (7)	16 (32)

3.2 Combined Analysis of SE-866/10 and SE-866/10-01:

This submission included an analysis of SE-866/10, a 645 patient one-year, randomized, double-blind, placebo controlled trial, combined with SE-866/10-01, a 462 patient 52 week extension of study SE-866/10. In between these two studies was a two week placebo period where the issue of drug withdrawal and rebound was explored (results can be found in the original review). The total duration of these studies, including the interim placebo period, was 102 weeks.

The primary objective was to determine long-term safety/tolerability via AE, BP/HR measurements, labs and ECGs. The analysis set consisted of all patients enrolled in SE-866/10-01. If BP was uncontrolled on monotherapy, then HCTZ, as previously mentioned, was added. If the BP remained high on HCTZ 25 mg added to CS-866, then the patient was withdrawn from the trial.

Table 8. Withdrawals during SE-866/10 and SE-866/10-01 by Reason (safety set of SE-866/10)

N (%)	CS-866			Placebo
	5 mg	10 mg	20 mg	
AE	13 (7)	8 (5)	2 (3)	10 (11)
Concomitant med	1 (0.6)	2 (1)	1 (0.6)	0
Lack of efficacy	11 (6)	6 (3)	6 (4)	18 (19)
Withdrew consent	2 (1)	8 (5)	10 (6)	8 (9)
Other	8 (5)	11 (6)	6 (4)	5 (5)
AE and lack of efficacy	0	0	0	1 (1)
AE and other	1 (0.6)	0	0	0
Lack of efficacy and other	0	0	0	1 (1)

Withdrew consent and lack of efficacy	0	0	0	1 (1)
Total withdrawn	36 (20)	35 (20)	28 (16)	44 (47)
Not withdrawn	142 (80)	142 (80)	143 (84)	49 (53)
Total	178	177	171	93

Demographic information: All patients were Caucasian. There was a smaller percentage of females in the CS-866 10 mg (37%) compared to placebo (49%). Median age was 59-61 years, mean height was about 167-168 cm, mean weight was about 77-80 kg and mean BMI was about 28-29 kg/m2. Duration of hypertension was 3.9-4.6 years. There was a higher percentage of smokers (25%) in placebo compared with those on CS-866 10 and 20 mg (14-15%).

Exposure: Study drug exposure is displayed below. The median exposure time was 728 days across all treatment groups. The placebo group showed the lowest mean exposure.

Table 9. Exposure to CS-866 and placebo (excludes 2 week interim placebo period) (analysis set)

Treatment	CS-866 5 mg (N=136)	10 mg (N=137)	20 mg (N=136)	Placebo (N=53)
Mean (SD) exposure (days)	717 (57)	705 (83)	703 (82)	681 (113)
Range (days)	391-784	363-799	378-769	365-804

The placebo group showed the highest mean exposure to HCTZ (median exposure was 443 days in placebo). Median exposure was 0 in the CS-866 treatment groups; the lowest mean exposure occurred in the CS-866 20 mg group. These results are consistent with the higher need for HCTZ in the placebo group.

Table 10. Exposure to HCTZ (excludes 2 week interim placebo period) (analysis set)

Treatment	CS-866 5 mg (N=136)	10 mg (N=137)	20 mg (N=136)	Placebo (N=53)
Mean (SD) exposure (days)	240 (314)	211 (302)	136 (261)	333 (323)
Range (days)	0-675	0-701	0-678	0-683

Safety/Tolerability:
Most common treatment-emergent adverse events (>5% in any CS-866 group) included: back pain, headache, influenza-like symptoms, gastroenteritis, hypertriglyceridemia, bronchitis, inflicted injury, UTI, hyperuricemia, pharyngitis, dizziness, vertigo, GGT increased, arthritis.

Deaths: Please see Table 4 (above). There was one death in a patient on 5 mg CS-866.

Serious adverse events (excluding deaths): Per Table 15.3.3, eight patients on CS-866 5 mg, 6 patients on CS-866 10 mg, 7 patients on CS-866 20 mg, and 6 placebo patients developed serious adverse events (excluding deaths). A review of these serious adverse events did not reveal any new/unusual/dose-related patterns.

Laboratory adverse events: No patient in the placebo group developed AE related to increased liver enzymes; the highest percentage of patients with increased GGT (5.9%) occurred in the 20 mg CS-866 group. About 2% of Cs-866 patients experienced an AE due to increased SGPT; the highest incidence of AE due to increased SGOT was seen in the CS-866 5 and 10 mg groups. There was only one discontinuation (in the CS-866 5 mg group) due to an elevated GGT.

BP/HR measurements: Small (< 3 bpm) mean decreases in heart rate were seen in all treatment groups, including placebo, between baseline and the final visit. No relationship to dose was seen. There were > 15 mm mean

decreases from baseline to the final visit in mean sitting DBP and SBP for all treatment groups (including placebo). These means include patients receiving monotherapy as well as the combination with HCTZ. Only one patient (on CS-866 10 mg) was withdrawn from the study due to treatment failure during the second year.

Reviewer comments:
1. Treatment-emergent adverse events appear consistent with the draft labeling proposed by the agency.
2. There appears to be an increased incidence of elevated GGT in the olmesartan group compared to placebo; however, there are few patient withdrawals due to elevated liver enzymes. This finding is consistent with the draft labeling as proposed by the Agency.

3.3. SE-866/24:
Title: The Effect of the Combination of the Oral Angiotensin II-Antagonist CS-866 and Pravastatin on Pharmacokinetics, Safety, and Tolerability in Healthy, Male Subjects

This was an open-label, single-site 3-way crossover study in 24 healthy male subjects. Each subject received, in random order: CS-866 20 mg (treatment A), pravastatin 20 mg (treatment B) or CS-866 20 mg with pravastatin 20 mg (treatment C) for seven days, separated by a 7-day washout period between treatments.
The primary objective was to assess effects on plasma pK parameters of CS-866 alone, pravastatin alone, and both drugs coadministered at steady state. Secondary objectives were: 1. urinary pharmacokinetic parameters for RNH-6270, pravastatin and RMS-416 (main metabolite of pravastatin) after multiple dosing, and 2. Safety/tolerability using EKG, BP, pulse, lab tests and AE monitoring.

Results: Twenty-four subjects were enrolled and completed the trial. There were no major protocol violations.
For the primary objective, coadministration of CS-866 and pravastatin lead to increases in variability in plasma levels. Mean steady state bioavailability of RNH-6270 was about 25% lower during treatment C compared to treatment A. Mean steady state bioavailabilities or pravastatin and RMS-416 were 21 and 13% lower during treatment C compared to treatment B.

Safety: There were no serious adverse events in this study. Most frequent AE were: SGPT increased (17 cases in 10 subjects), headache (4 cases in 4 subjects) and SGOT increased (3 cases in 3 subjects). There were no significant safety issues identified by changes EKG or vital signs. Of the increased SGPT cases, 6 occurred during treatment A, 4 occurred during treatment B, and 7 occurred during treatment C. Except for 2 patients in treatment C (where the increased SGOT was "moderate"), the increased SGPT was classified as "mild." One patient in treatment C experienced an increased GGTP.

Reviewer Comments:
1. A comparison of the co-administered (olmesartan + pravastatin) treatment vs. each drug given alone resulted in a failure to meet the acceptance range for bioequivalence. This result suggests an interaction between olmesartan and pravastatin; the clinical significance of this interaction is unclear and has not been explored further in this study.
2. There were no withdrawals or serious adverse events in this study.
3. Both olmesartan and pravastatin appeared to be well tolerated in this study.

3.4 SE-866 CMB/01:
Title: The Effect of the Combination of the Oral Angiotensin II-Antagonist CS-866 and Hydrochlorothiazide on Pharmacokinetics, Safety, and Tolerability in Healthy, Male Subjects

This was an open-label, single-site 3-way crossover study in 24 healthy male subjects. Each subject received, in random order: CS-866 20 mg (treatment A), HCTZ 25 mg (treatment B) or CS-866 20 mg with HCTZ 25 mg (treatment C) for seven days, separated by a 7 to 14-day washout period between treatments.

The primary objective was to assess influences of each drug on the pharmacokinetics of the other drug. Secondary objectives were to evaluate urine pK parameters after multiple dosing and assess safety/tolerability of the different treatments.

Results: Twenty-four male volunteers were enrolled. One patient was withdrawn due to SAE (fractured nasal bone); 23 subjects completed the trial.

Pharmacokinetic results:
Results of pharmacokinetic parameters showed, via statistics, an interaction between CS-866 and HCTZ at the doses studied. The clinical significance of this interaction is unclear.

Table 11. Pharmacokinetic results (Valid cases set, N=23)

Parameter	Substance	Treatment comparison	90% CI	Equivalence acceptance range	Bioequivalence
AUC	RNH-6270	C vs. A	(0.67, 1.55)		No
	HCTZ	C vs. B	(0.58, 1.08)		No
Cmax	RNH-6270	C vs. A	(0.60, 1.64)		No
	HCTZ	C vs. B	(0.60, 1.04)		No
Tmax	RNH-6270	C vs. A	0		Yes
	HCTZ	C vs. B	0		yes

Source: Sponsor. Treatment A=CS-866 20 mg; Treatment B= HCTZ 25 mg; Treatment C= CS-866 20 mg plus HCTZ 25 mg.

The sponsor has noted a high between-subject variability in plasma and urine pharmacokinetic parameters for both drugs. When the sponsor excluded 6 subjects with anomalous PK profiles and reanalyzed the data, the sponsor was able to demonstrate AUC and Cmax within the equivalence acceptance range.

Most frequent AEs were headache (4 cases in 3 subjects) and SGPT increased (4 cases in 2 subjects). Assessment of vital signs, physical examinations and EKGs did not reveal abnormalities of concern. Systolic and diastolic blood pressures were normal throughout the trial.

Reviewer Comments:
1. There was high between-subject variability in AUC and Cmax.
2. For the valid cases set (N=23), the 90% confidence intervals fell outside accepted criteria for equivalence. There may be an interaction between CS-866 and HCTZ at the doses studied; the clinical significance is unclear.
3. Both CS-866 and HCTZ were well tolerated.

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/s/

Shari Targum
2/25/02 12:21:56 PM
MEDICAL OFFICER

NDA # 21-286

MEDICAL REVIEW OF EFFICACY AND SAFETY

BENICAR
(OLMESARTAN MEDOXOMIL)

SANKYO PHARMA INC.,
NEW YORK, NEW YORK

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
(HFD 110)

June, 2001

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MEDICAL REVIEW OF EFFICACY AND SAFETY

S.Rodin, M.D.
S.Targum, M.D.
A.O.Williams, M.D.

0.0 Executive summary

- The sponsor has submitted NDA 21-286 for BENICAR, an AII antagonist, for the treatment of hypertension. The clinical development program involved 2,693 hypertensive patients administered 2.5mg to 80mg of this pro-drug, olmesartan, and placebo.

- BENICAR was shown to be effective in lowering diastolic blood pressure over the dose range of 5mg to 80 mg. There was limited exposure to doses over 20 mg. There was no effect on age but there were some effects on sex and race.

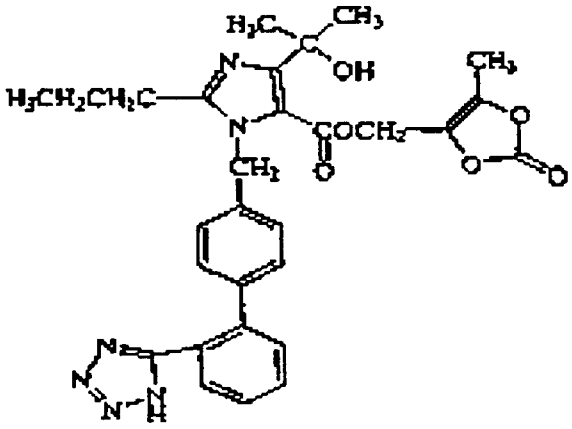
- The most common treatment emergent adverse event in the placebo-controlled monotherapy trials was dizziness, a common feature to other sartans (e.g. valsartan, losartan, and candesartan). Furthermore, dizziness and angina were the commonest adverse events leading to discontinuations during the phase 2/3 studies. Other adverse events experienced by patients during the trials include elevated CPK and hepatic enzyme levels. These safety issues should be reflected in the package insert.

- At the present time, we estimate Benicar's therapeutic benefit to risk relationship as being acceptable for the proposed patient population. We also estimate that the placebo-controlled clinical studies have demonstrated adequate efficacy (20mg to 40 mg once daily dosing) for the proposed indication of lowering blood pressure.

- We recommend that Benicar be approved subject to establishing that Benicar is not mutagenic and that other safety issues that may be of concern are indicated in the package insert.

1.0 Introduction
Pharmacologic type: Angiotensin antagonist
NDA submission date: 25 July 2000
Center Receipt date: 26th July 2000
Reviewer's receipt date: 27th July 2000
Sponsor: Sankyo Pharma. Inc
Code Name: CS-866
Generic Name: Olmesartan medoxomil
Trade Name: Benicar
CS-866 and Olmesartan are used interchangeably in this review.

1.1 Chemical name and structure
Olmesartan medoxomil is described chemically as (5-methyl-2-oxo-1,3-dioxolen-4-yl) methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1 [[2'-(1H-tetrazol-5-yl) biphenyl-4-yl]methyl] imidazol-5-carboxylate.
Olmesartan medoxomil is a white to light yellowish-white powder or crystalline powder with a molecular weight of 558.59. It is practically insoluble in water and sparingly soluble in methanol.
Its empirical formula is $C_{29}H_{30}N_6O_6$ and its structural formula is:



Proposed clinical indication: Treatment of hypertension
Route of administration: Oral
1.2 Mode of Action: "CS-866 is a novel, orally active angiotensin (Ang) II antagonist. It is a pro-drug that is deesterified to its active metabolite. The active metabolite of CS-866, RNH-6270, blocks the vasoconstrictor effects of Ang II by selectively blocking its binding to AT1 receptor, which is found in many tissues, including vascular smooth muscle."
Angiotensin II receptor blockers, with increased specificity and selectivity in blocking the circulating and tissue effects of Angiotensin II at the receptor level, would have potential

advantages over ACE inhibitors, including a lower incidence of bradykinin-related adverse events such as cough or angioedema.

1.3 Animal Pharmacology/Toxicology
High doses of CS-866 decreased renal blood flow, glomerular filtration rate and fractional filtration. CS-866 also induced microscopic changes in the kidney characterized by juxtaglomerular cell hyperplasia and renal tubular epithelial regeneration with thickening of the tubular basement membranes. Histopathological findings in the kidney included juxtaglomerular cell hyperplasia, an increase in the juxtaglomerular cell granulation index (JGI), and regeneration of tubular epithelium accompanied by thickening of the basement membrane. A perinatal/postnatal toxicity study in rats demonstrated that CS-866 produced an inhibitory effect on postnatal development. (See Pharmacologic/Toxicologic review section).

1.5 Proposed labeling: Dosage forms: Optimal therapeutic dose range = 20-40 mg QD (With and without HCTZ).

1.6 Adequacy of clinical studies for efficacy of CS-866
Based on a total of 2,693 patients, the primary analysis group, in the controlled clinical studies, the population is considered adequate for analysis of efficacy (Table 1). Appendix 1 is a sample of inclusion criteria for the clinical controlled studies in this NDA.

1.61 Demographics for integrated review of efficacy
The demographics are presented in Table 2 below. There is a preponderance of Caucasians in the study (88.5% in the placebo and 91.5% in the treated group). Relatively small numbers of blacks and other non-Caucasian groups may explain the significant differences in these populations as noted in individual studies and the integrated summary of efficacy.

Comparisons within the demographic groups and strata using an ANCOVA model with centralized baseline vital signs as a covariate, and study, treatment, demographics (gender, age, or race) as factors, and treatment by demographic group interaction term were performed. For ambulatory blood pressure monitoring (ABPM) data, the p-values reported for the comparisons were adjusted for multiplicity using the Dunnett procedure with a family-wise error rate bounded by 0.05.

1.7 Demographics: Tables 1&2 present total number and demographics of patients exposed to CS–866 monotherapy, respectively.

Table 1: Patients on CS-866 monotherapy

Study #866-	Placebo	CS-866	Total	1^0 study time point
204	47	136	183	Week 8
305	90	431	521	Week 8
06	26	50	76	Week 6
09	110	681	791	Week 12
11	71	221	292	Week 12
306	115	113	228	Week 8
10	89	513	602	Week 12
Total	548	2145	2693	

Table 2: Demographics at study entry - ITT population

	Placebo	CS-866
Gender N(%)		
Male	311(56.8%)	1113(51.9%)
Female	237(43.2%)	1032(48.1%)
Race		
Caucasian	485(88.5%)	1955(91.5%)
Black	26(4.7%)	74(3.4%)
Hispanic	32(5.8%)	106(4.7%)
Asian	2(0.4%)	7(0.3%)
Other	3(0.5%)	3(0.1%)
Age, Years	N=548	N=2145
Mean±SD	55.2±10.94	55.7±11.47
<65	440(80.3%)	1681(78.4%)
>65	108(19.7%)	464(21.6%)
SiDBP	NS (N=548)	NS(N=2145)
StDBP	NS (N=548)	NS(N=2145)
Pulse rate	NS (N=548)	NS (N=2145)
Total N for efficacy = 2, 693		
Height/ weight	NS	NS

The study medication to establish efficacy of CS 866 is presented in Table 3.
NS=Not significant

1.8 Antihypertensive effects of CS–866 Monotherapy

The 7 clincal controlled studies used to establish efficacy include CS #866-204,305,06, 09 and 11 with CS-866 monotherapy, and CS # 866-10 and 306 with CS-866 and additional HCTZ therapy. All the patients had been diagnosed with essential hypertension (Mean sitting dBP >95 mm Hg at any 2 consecutive visits or > 105 mm Hg at any one visit). The duration of the studies, randomized and placebo-controlled, varied from 6 to12 weeks for short term and up to 12 months for long term evaluation (Table 4). Doses ranged from 2.5mg - 80 mg. Three studies, #204, 06, &11, used ABPM for primary end point (Table 3).

Table 3: Controlled clinical trials of effectiveness and dosing regimen

	Studies #	Dose	Primary time point	Open Label
Short term Monotherapy Comparator	204,305,306, 06,09,10,11 17,18,*19,20	2.5mg - 80mg See Tables 4/5	6-12weeks	- -
Long Term	305,306,10, *19	CS-866 +HCTZ (12.5mg-25mg)	-	12 weeks to 12 months; option of HCTZ titration
ABPM	204 (bid), 06, and 11 (o.d)	2.5mg to 80mg	6-12 weeks	-
*Study 19-patients had moderate to severe hypertension. Comparator = Losartan. Duration of study = 24 weeks				

Table 4: Objectives of studies in controlled clinical studies of efficacy- CS-866

Study/ Country	DESIGN	Objective	N CS 866	N Plcbo	Drug regimen	Duration *Population
866-204 US	R,DB,PC,ABPM	Dose ranging Safety/ Efficacy	286/281	48/47	5,20, 80 mg od placebo or 2.5,10,40mg, bid, plcbo	8 weeks FDM
305 US	R,DB,PC,ABPM	Safety and efficacy	435/429	91/88	2.5,5,10,20,40mg, plcbo 2.5,5 10,20,40mg, plcbo	1 year FD/HCTZ
306 US	R,DB,PC, ABPM Dose titration	Safety and efficacy	341/337	116/114	5,10,20mg, plcbo or 20mg,40mg HCTZ	8 weeks plus 4 months TDM
06 EU	R,DB,PC, ABPM	Safety and efficacy	50/50	26/26	20,80mg od, plcbo	6 weeks FDM
09 EU	R,DB,PC,ABPM	Safety and efficacy	682/680	110/110	2.5,5,10,20,40,80mg od plcbo	12 weeks FDM
10 EU	R,DB,PC, ABPM	Safety and efficacy	526/511	93/89	5,10,20,od plcbo 5,10,20,od + HCTZ,plcbo	12 weeks 40 weeks FD/HCTZ
EU	R,DB,PC,	Safety and efficacy	526/454	53/50	Placebo	2 weeks FD/HCTZ
11 EU	R,DB,PC,	Safety and efficacy	221/219	71/68	2.5,5,10mg od plcbo	12 weeks FDM
17 EU	R,DB,PC,	Safety and efficacy	164/164	164/164	10, 20mg CS ,od +HCTZ 50,100mg Atenolol+HCTZ	12 weeks 12 weeks C

Study/ Country	DESIGN	Objective	N CS 866	N Plcbo	Drug regimen	Duration *Population
18 EU	R,DB,PC,	Safety and efficacy	165/165	161/161	10,20mg CS od 50,100mg Atenolol od	12 weeks 12 weeks C
19 EU	R,DB,PC,	Safety and efficacy	160/158	156/152	10,20mg od 50,100mg losartan od + HCTZ	12 weeks 12 weeks C
20 EU	R,DB,PC,	Safety and efficacy	148/148	143/143	5,10,20mg CS od 12.5,25,50mg captopril bid	12 weeks 12 weeks C

R=randomized, DB=double blind, PC=placebo-controlled, ABPM=Ambulatory BP measurements OL=open label, PL=parallel group, DT=dose titration,SE=Safety and efficacy. * Population: essential hypertension. Trough-to-peak ratios were only analyzed in #204,10 &11. ABPM data available- Study #866-06. FDM=Fixed dose monotherapy; TDM=Titrated dose monotherapy; C=Comparator. FD/HCTZ=Fixed combination with HCTZ.

1.9 Studies on CS-866 monotherapy and comparators (Tables 5-6).

Table 5: Actively controlled clinical studies - 866- Integrated review of efficacy

Study/ Country	DESIGN	Objective	No. CS 866	Patient	Drug regimen and comparator	Duration
#18	R,DB,PL,DD,	Efficacy	326	HY	Atenolol	Week 12
#19	R,DB,PL,DD,	Efficacy	316	HY	Losartan	Week 12
#20	R,DB,PL,DD,	Efficacy	291	HY	Captopril	Week 12
#17	R,DB,PL,DD,	Efficacy	328	MS-HY	Atenolol +HCTZ	Week 12

HY=Hypertension; MS-HY= Moderate-to-severe hypertension

The only uncontrolled study in this NDA is SE-#14 (Table 6a).

Table 6a: Uncontrolled study SE- #866-14

Study	ANALYTE	Objective	N	Review conclusion
866-14 USA	RNH-6270	Pharmacokinetics	HY	P<0.03, young versus very elderly

Table 6b: Summary Table of studies during the Olmesartan development program

Bioavailability/Bioequivalence	Protocol	N	n•	Dose (mg)	Exposure
A Randomized, Open Label, Four-Way Crossover Study Using Single Doses of RNH-6270 Solution Intravenously, RNH-6270 Solution Orally, CS-866 Tablets Orally and CS-866 Suspension Orally to assess Bioavailability in Healthy Adult Volunteers	866-108	24	24	20 (tab), 20 (PO susp), 16 RNH-6270 (iv), 16 RNH-6270 PO	Single dose, Crossover (4x)
A Radio-labelled, Pharmacokinetic and Dose Recovery Study of the [14]C-labelled Oral Angiotensin II-Antagonist CS-866 in Healthy, Adult Volunteers	SE-866/13	6	6	20	Single dose
A Randomized, Open-Label, Two-Way Crossover Bioequivalence Study of CS-866 Tablets in Healthy Adult Volunteers	866-116	30	30	20 (different formulations)	Single dose, Crossover (2x)
Bioequivalence Study of CS-866 Tablets (2.5, 10 and 20 mg) in Healthy Male Volunteers	SE-866/12	24	24	20 (total dose, administered as different formulations)	Single dose, crossover (4x)
Bioequivalence Study of CS-866 Tablets (10 mg) in Healthy, Male Volunteers	SE-866/22	24	24	10 (different formulations)	Single dose, Crossover (4x)
Pharmacokinetic (PK) Studies					
Baseline PK Studies, Initial Safety and Tolerability: Healthy Volunteers					
A Randomized, Double-Blind, Placebo-Controlled Ascending, Single Dose, Tolerance Study of Oral CS-866 in Healthy Adult Male Volunteers	866-101	40	25	10, 20, 40, 80, 160	Single dose
A Randomized, Double-Blind, Placebo-Controlled Ascending, Multiple Dose, Safety and Tolerance Study of Oral CS-866 in Healthy Adult Male Volunteers	866-102	30	30	20, 40, 80	Multiple dose (10 days)
An Open-Label, Ascending Single Dose, Safety and Tolerance Study of Intravenously Administered RNH-6270 in Healthy	866-107	34	34	1, 2, 4, 8, 16, 32 RNH-6270	Single dose

ioavailability/Bioequivalence	Protocol	N	n•	Dose (mg)	Exposure
Adult Male Volunteers				(iv)	
Tolerability and Safety of the Angiotensin II-Antagonist CS-866 in Healthy, Male Subjects (Single Dose)	SE-866/01	63	42	10, 20, 40, 80, 160, 240, 320	Single dose
Tolerability and Safety of the Angiotensin II Antagonist CS-866 in Healthy, Male Subjects (Multiple Dose)	SE-866/02	24	18	40, 80	Multiple dose (14 days)
A Pharmacokinetic Dose Proportionality Study Following Multiple Daily Doses of 2.5, 5, 10, 20 and 40 mg CS-866 in Healthy Volunteers	SE-866/21	30	30	2.5, 5, 10, 20, 40	Multiple dose (7 days), Crossover (5x)
Phase I Clinical Study of CS-866 - Preliminary Investigation	141-010	10	10	1, 2, 4, 8, 16, 32	Single dose
Phase I Clinical Study of CS-866 - Single Administration in Fasting	141-011	27	18	4, 8, 16,	Single dose
Phase I Clinical Study of CS-866 - Repeated Administration	141-041	10	7	16	Multiple dose (7 days)

•n=received olmesartan (CS-866)

	Protocol	N	n•	Dose (mg)	Exposure
Phase I Clinical Study of CS-866 - 40 mg Repeated Administration Study	143-005	10	7	40	Multiple dose (8 days)
Phase I Study of CS-866 - Determination of Unchanged Compound in Blood and Glucuronide in Urine from Healthy Volunteers – A Pilot Study in Healthy Volunteers	GR 142-026	??	??	8, 16, 24	??
Population Subsets(Intrinsic Factors)					
A Comparative Pharmacokinetic Study of CS-866 Tablets and RNH-6270 Intravenous Solution Administered to Patients with Impaired Liver and Healthy Volunteers	866-109	24	24	10 (PO CS-866), 8 (IV RNH-6270)	Single dose (PO), then 10 day washout followed by single dose (iv)
A Comparative Pharmacokinetics Study of CS-866 Tablets in Healthy Adult Male and Female Volunteers	866-110	35	35	20	Single dose
Multiple Dose Tolerability, Safety and Pharmacokinetic Study of the Angiotensin II-Antagonist CS-866 in Young and Elderly Hypertensive Patients	SE-866/07:	37 ‡	24	80	Multiple dose (10 days)
A Pharmacokinetic, Safety and Tolerability Study of the Oral Angiotensin II-Antagonist CS-866 in Young and Very Elderly Patients with Mild to Moderate Essential Hypertension	SE-866/14:	44 †	36	10	Multiple dose (14 days)
A Comparative Pharmacokinetic, Safety and Tolerability Trial of the Oral Angiotensin II-Antagonist CS-866 in Subjects with Varying Degrees of Renal Impairment and Healthy Volunteers	SE-866/16	34	34	10	Multiple dose (7 days)
Population Subsets (Extrinsic Factors)					
A Comparative Bioavailability Study of CS-866 Tablets in the Presence and Absence of Food in Healthy Adult Male Volunteers	866-103	25	25	20	Single dose, crossover (3x)
The Effect of an Antacid (Aluminium Magnesium Hydroxide) on the Pharmacokinetics and Safety of the Oral Angiotensin II- Antagonist CS-866 in Healthy Male Subjects	SE-866/05	24	24	20	Multiple dose (5 days), crossover (2x)
The Effect of the Combination of the Oral Angiotensin II-Antagonist CS-866 and Warfarin on	SE-866/08	26 *	24	40	Multiple dose (7 days), Crossover (2x)